Obstruction in Hypertrophic Cardiomyopathy: Many Faces

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Hypertrophic cardiomyopathy (HCM), the most common inherited cardiomyopathy, exhibits left ventricular hypertrophy not secondary to other causes, with varied phenotypic expression. Enhanced actin-myosin interaction underlies excessive myocardial contraction, frequently resulting in dynamic obstruction within the left ventricle. Left ventricular outflow tract obstruction, occurring at rest or with provocation in 75% of HCM patients, portends adverse prognosis, contributes to symptoms, and is frequently a therapeutic target. Transthoracic echocardiography plays a crucial role in the screening, initial diagnosis, management, and risk stratification of HCM. Herein, we explore echocardiographic evaluation of HCM, emphasizing Doppler assessment for obstruction. Echocardiography informs management strategies through noninvasive hemodynamic assessment, which is frequently obtained with various provocative maneuvers. Recognition of obstructive HCM phenotypes and associated anatomical abnormalities guides therapeutic decision-making. Doppler echocardiography allows monitoring of therapeutic responses, whether it be medical therapies (including cardiac myosin inhibitor therapy) or septal reduction therapies, including surgical myectomy and alcohol septal ablation. This article discusses the hemodynamics of obstruction and practical application of Doppler assessment in HCM. In addition, it provides a visual atlas of obstruction in HCM, including high-quality figures and complementary videos that illustrate the many facets of dynamic obstruction. (J Am Soc Echocardiogr 2024;37:613-25.)

Keywords: Hypertrophic cardiomyopathy, Echocardiography, Doppler, Left ventricular outflow tract obstruction, Myectomy

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy, characterized by complex phenotypic and genetic expression.[1] Even within a single HCM family pedigree, there can be tremendous variability in phenotype that spans clinical, anatomic, hemodynamic, and arrhythmogenic features. On a molecular basis, enhanced actin-myosin interaction results in excessive myocardial contraction and simultaneous impairment in diastolic relaxation.[2] Downstream sequelae of excessive shear forces and abnormal loading conditions constitute one proposed mechanism for the development of pathologic hypertrophy. Hypertrophy is most frequently asymmetric, involving the ventricular septum, but can occur in any pattern. Mitral valve (MV) abnormalities are relatively common and include hypertrophy or displacement of the papillary muscles, abnormal attachment of the chordae tendinea with excessive anterior positioning, and elongation of the anterior mitral leaflet.[3,4] Left ventricular (LV) outflow tract (LVOT) obstruction at rest or with provocation is present in 75% of patients with HCM. Recently, Mitchell *et al.*[5] constructed a practical echocardiographic framework for HCM imaging. In that important article, they provided guidance on image acquisition, measurement techniques, and detailed technical considerations for many aspects of HCM assessment, including the assessment of obstruction, diastolic dysfunction, and response to both medical and invasive therapies.[5] The purpose of this manuscript is to provide further echocardiographic exploration of HCM, with a particular focus on Doppler assessment of obstruction.

Recognition of the different obstructive HCM phenotypes (dynamic LVOT obstruction, midventricular obstruction [MVO], combined LVOT and MVO) and anatomical abnormalities that predispose to obstruction has management implications.[6-8] Transthoracic echocardiography (TTE) remains the imaging test of choice for initial diagnosis, noninvasive assessment of hemodynamics, and monitoring of pharmacologic and septal reduction therapy and along with cardiac magnetic resonance imaging (CMR) has a prognostic role for sudden cardiac death risk ascertainment in HCM.

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Abbreviations

2D = Two-dimensional

3D = Three-dimensional

CMR = Cardiac magnetic resonance imaging

CWD = Continuous-wave Doppler

HCM = Hypertrophic cardiomyopathy

LV = Left ventricular, ventricle

LVH = Left ventricular hypertrophy

LVOT = Left ventricular outflow tract

MR = Mitral regurgitation

MV = Mitral valve

MVO = Midventricular obstruction

PWD = Pulsed-wave Doppler

SAM = Systolic anterior motion

TEE = Transesophageal echocardiography

TTE = Transthoracic echocardiography

A plethora of different conditions may mimic the phenotype of HCM on TTE. Phenocopies span physiologic LV hypertrophy (LVH) such as athlete's heart, pressure LVH in the setting of increased afterload (hypertensive heart disease, fixed subaortic stenosis, valvular aortic stenosis, supra-aortic membrane), storage disorders such as Fabry cardiomyopathy, and infiltrative disease most commonly in the form of cardiac amyloidosis.[1,7,9,10] Furthermore, it is possible to have overlap in conditions, particularly with regards to systemic hypertension in HCM, which is present in nearly half of some large cohorts.[11] Although dynamic ventricular obstruction and systolic anterior motion (SAM) should increase clinical suspicion of obstructive HCM, these features are not pathognomonic and may manifest in various phenocopies dependent on distribution of wall thickening. In athlete's heart, LVH is usually symmetrical, rarely exceeds 14 mm, and does not typically result in SAM or LVOT obstruction.[7] Hypertensive heart disease may result in both SAM and LVOT obstruction related to the development of a septal bulge,[7] particularly if hypertension is severe, long-standing, and untreated.[10] One feature suggestive of hypertensive heart disease is the occurrence of SAM at end systole, a phenomenon known as "pseudo" SAM.[12] Elderly patients may present with a prominent basal septal bulge, which can predispose to LVOT obstruction,[13] particularly in the context of profound kyphosis, which exacerbates LVOT-aortic angulation. Although the degree of focal LVH in this condition is frequently mild, differentiation of elderly basal septal bulge from HCM requires clinical context. Our approach to obstruction in this scenario parallels that of dynamic LVOT obstruction in HCM, largely focused on lifestyle modifications, avoidance of unnecessary lowering of preload or afterload, and prudent use of beta-blockade. Echocardiographic features differentiating Fabry cardiomyopathy, cardiac amyloidosis, glycogenosis, and Noonan syndrome have been detailed elsewhere.[9] However, the integral role of multimodality imaging and genetic testing in cardiomyopathic diagnosis, whether via CMR or positron emission tomography computed tomography, is important to emphasize. Noonan syndrome is more likely to have right-sided dynamic obstruction. However, dynamic LV obstruction can be present in each of these conditions, with similar hemodynamic underpinning despite vastly different myocardial substrates.

DYNAMIC LEFT VENTRICULAR OUTFLOW OBSTRUCTION

The mechanism of dynamic obstruction in HCM is a complex interplay of MV and subvalvular apparatus abnormalities,[14-16] septal hypertrophy, and narrowing of the LVOT,[16] as well as steep and/or

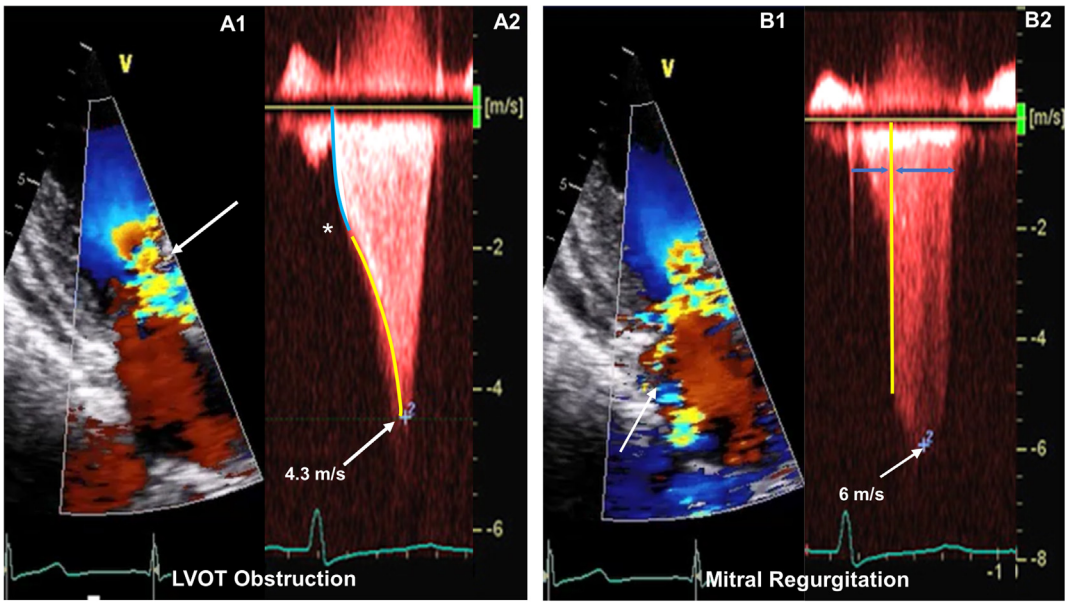

Figure 1 Color-flow Doppler shows aliasing at the site of LVOT obstruction (**A1**, *arrow*). Continuous-wave Doppler demonstrates an initial convex contour during early systole when flow is unimpeded. The CWD envelope transitions (*) to a concave contour as mitral leaflet SAM progressively increases during systole (**A2**, *arrow*). The Doppler peak instantaneous LVOT gradient ($4\,V^2 = 4\,(4.3\ \text{m/sec})^2 = 74$ mm Hg) corresponds with invasive peak-to-peak pressure gradients. Color-flow Doppler of "classic" SAM-mediated MR is posteriorly directed (**B1**, *arrow*) with a peak CWD velocity in mid-late systole (**B2**, *arrow*). The peak MR velocity always exceeds the peak LVOT velocity and can be used to calculate the LVOT gradient when the LVOT Doppler signal is contaminated by MR.
$(\text{LV to LA gradient}) = 4(\text{MR velocity})^2 = 4(6\ \text{m/s})^2 = 144$ mm Hg.
$\text{LVOT gradient} = (\text{LV to LA gradient}) + (\text{Assumed LA pressure}) - (\text{Systolic blood pressure})$.
$\text{LVOT gradient} = 144\ \text{mm Hg} + 15\ \text{mm Hg} - 90\ \text{mm Hg} = 69\ \text{mm Hg}$.

HIGHLIGHTS

- Doppler allows for evaluation of LVOT, midventricular, and multilevel obstruction.
- An organized approach is needed for dynamic LVOT obstruction provocation.
- Doppler evaluation is integral for HCM myosin inhibitor management.
- TTE guides septal reduction therapy (SRT) candidacy, intraprocedural assessment, and post-SRT follow-up.

anteroseptal angulation of the outflow tract.[17,18] Outflow tract obstruction is present at rest in about one-third of HCM patients. However, in many patients, a systolic LV gradient is only elicited with physical exertion or maneuvers that alter loading conditions. Obstruction in HCM can be extremely labile, varying significantly throughout the day or even within a single hemodynamic evaluation.[19] These observations have been incorporated into consensus criteria to classify HCM on the basis of obstruction: (1) resting obstruction (LVOT gradient ≥30 mm Hg), (2) latent obstruction (<30 mm Hg at rest, ≥30 mm Hg with provocation), and (3) nonobstructive (<30 mm Hg at rest and with provocation).[20] A gradient of 50 mm Hg at rest or with provocation identifies severe obstruction and often serves as a threshold for pursuing septal reduction therapy[20] or initiation of myosin inhibitor therapy. Papillary muscle malposition and MV leaflet elongation lead to laxity at the interface between the chordae and leaflets, facilitating SAM.[14,21] Vector flow mapping has elucidated that the mechanism by which abnormalities of the mitral apparatus facilitate dynamic LVOT obstruction is via drag flow on the MV during ventricular systole, as opposed to lift (Venturi effect).[22] Drag flow results in conformational changes of the large surface area anterior MV leaflet, resulting in approximation of mitral leaflet coaptation toward the ventricular septum and dynamic LVOT obstruction.[22-24] Importantly, SAM often begins in early systole, with the hypertrophied septum redirecting early low-velocity systolic flow below the MV and displacing it anteriorly, precluding Venturi effects as the dominant force initiating SAM-mediated LVOT obstruction.[14,25] This is further highlighted when examining the history of operative treatment for HCM. While limited basal myectomy aimed at relieving proposed LVOT Venturi effects proved suboptimal, extended myectomy, which abolishes drag forces, is an effective and reliable operative strategy.[26]

As SAM progresses, the LVOT becomes progressively narrowed, worsening LVOT obstruction, which in turn augments further SAM. Severity of LVOT obstruction is most commonly assessed by continuous-wave Doppler- (CWD-) derived peak instantaneous gradient (Figure 1A). Different mechanisms have been implicated in SAM and associated mitral regurgitation (MR), including abnormally elongated or hypertrophied papillary muscles, chordal thickening or elongation, anomalous papillary muscles inserting directly onto MV leaflets, increased mitral tenting volume, diminutive or

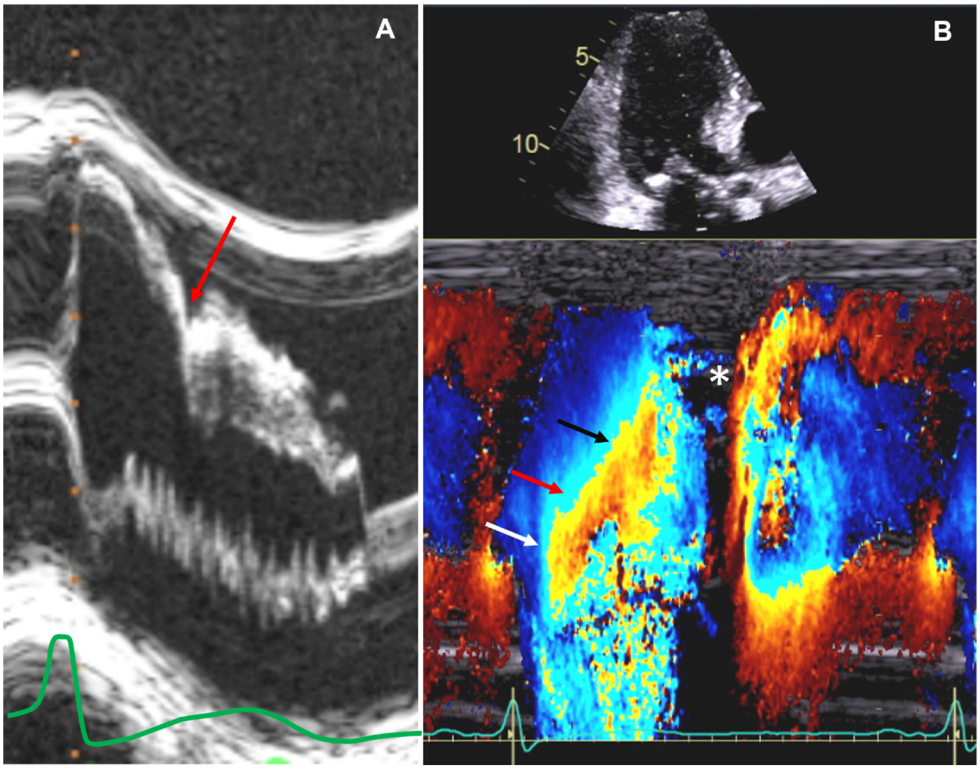

Figure 2 M-mode of the aortic valve demonstrates fluttering of the leaflets and midsystolic notching (*red arrow*) characteristic of obstructive flow dynamics **(A)**. Color M-mode **(B)** elicits timing and location of dynamic obstruction. During initial ejection (just after the QRS), flow is laminar (*white arrow*), correlating with a preserved carotid upstroke on exam. This is followed by acceleration of flow, turbulence, and aliasing within the LVOT during early systole indicative of dynamic obstruction (*red arrow*) followed by migration of the level of obstruction into the midventricle in late systole (*black arrow*). Lack of color, if present in systole, would represent cessation of flow such as cavitary obliteration. Following completion of systole, absence of color (*asterisk*) denotes isovolumetric relaxation.

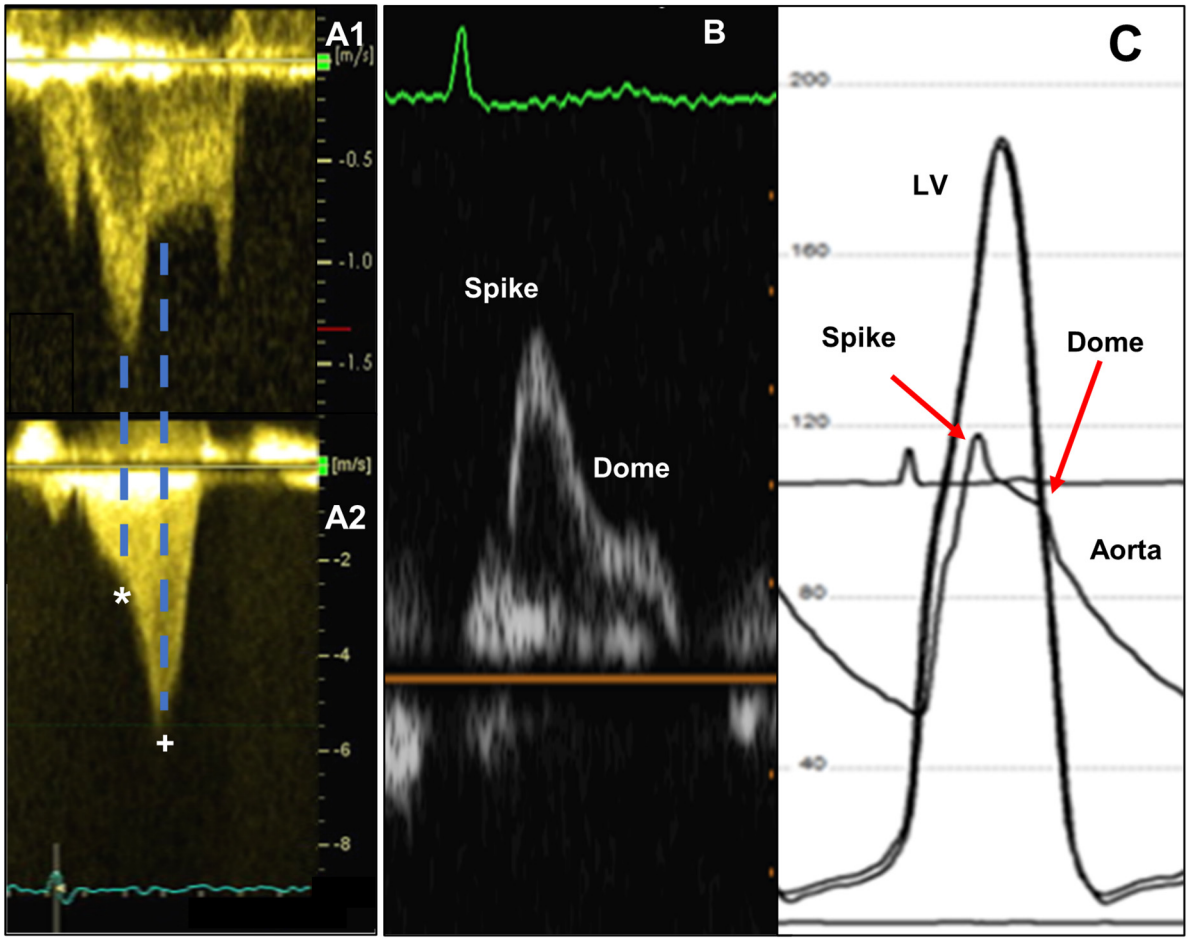

Figure 3 Pulsed-wave Doppler of systolic flow proximal to the site of severe LVOT obstruction shows a bifid profile (lobster-claw phenomenon) **(A1)**.[23] There is a rapid decline in the proximal flow velocities, which coincides with the LVOT CWD inflection point (*) and the onset of dynamic LVOT obstruction **(A2)**. The nadir of proximal flow velocities occurs at the time of maximal LVOT obstruction (+). Reemergence of proximal flow occurs as SAM of the mitral leaflets decreases. Pulsed-wave Doppler with a double-peak contour[6] in the abdominal aorta **(B)** and spike-and-dome (*arrows*) in the aortic pressure tracing **(C)** equate to the bifid peripheral pulse in patients with severe dynamic LVOT obstruction.

thickened leaflets, MV prolapse, and ruptured chordae.[14,15,21,27] Usually, the anterior and posterior MV leaflets fail to coapt in mid-late systole, due to the upward and anterior motion of the anterior leaflet toward the LVOT, creating a funnel that directs the MR posteriorly through the interleaflet gap. The degree of resting LVOT obstruction has been shown to be directly proportional to the degree of MR associated with SAM. Compared with the CWD contour of LVOT obstruction, the contour of SAM-mediated MR is more rounded with higher velocity, the latter of which reflects a much higher LV–to–left atrial gradient (Figure 1B). Dynamic LVOT obstruction can occur during exercise in the absence of LVH secondary to anatomical abnormalities of the MV leaflet and papillary muscles, which has surgical and prognostic implications.[28,29] Mitral annular calcification may also cause restricted movement of the mitral leaflets, leading to anterior displacement of the MV and further predisposing to LVOT obstruction.[30]

Systolic anterior motion classically results in a posteriorly directed MR jet (Video 1) with a peak CWD velocity in mid-late systole, but this finding has a low negative predictive value, and clinicians should be cautious in using MR jet direction on preoperative TTE to guide MV surgery decision-making during septal myectomy for HCM.[31] Primary MV disease may coexist with SAM, which usually results in a nonposteriorly directed jet of MR. Transesophageal echocardiography (TEE) is often helpful when there is uncertainty on the mechanism of MR by TTE. Also, phenylephrine provocation may be of benefit because it increases afterload, which attenuates SAM-related MR but not primary MR.[32]

M-mode remains a valuable echocardiographic tool for the assessment of obstruction, owing to its superior temporal resolution. M-mode in the parasternal long-axis view may assess for midsystolic notching of the aortic valve, reflecting very rapid ejection of LV stroke volume in early systole followed by attenuation of stroke volume in the obstructive phase (Figure 2A). Systolic anterior motion septal contact duration correlates with the severity of LVOT obstruction.[33] The degree of SAM can be classified as (1) mild (anterior mitral leaflet–septal distance >10 mm), (2) moderate (anterior mitral leaflet–septal distance ≤10 mm or mitral leaflet–septal contact lasting <1/3 of systole), or (3) severe (prolonged anterior leaflet–septal contact; ≥1/3 of echocardiographic systole).[33] Color M-mode also provides localization and timing of dynamic obstruction with high accuracy and is utilized regularly in our practice (Figure 2B). Color-flow Doppler allows for localization of turbulent, aliased blood flow

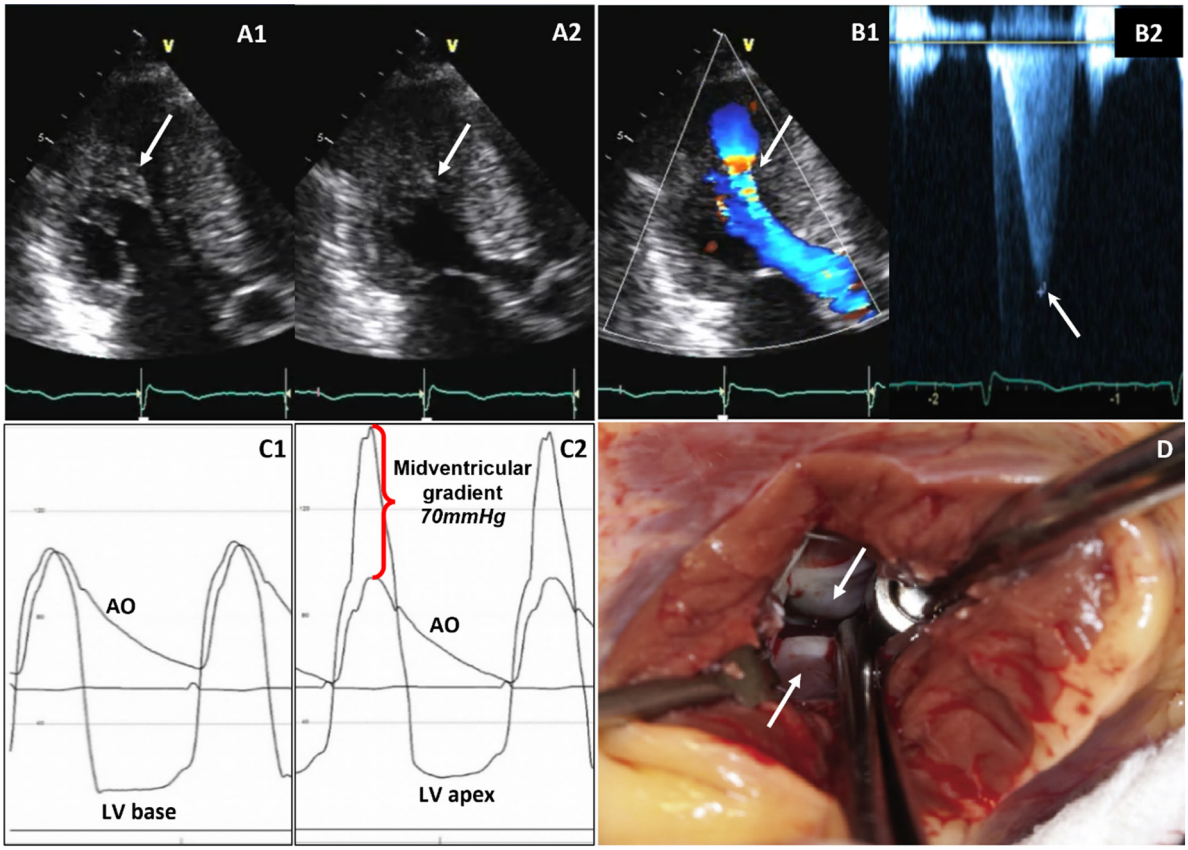

Figure 4 Midventricular obstruction caused by a prominent papillary muscle (**A1**, *arrow*), which abuts the hypertrophied septum during systole (**A2**, *arrow*, Video 2). Color-flow Doppler shows aliasing (turbulent flow) within the midventricle (**B1**, *arrow*, Video 3) that corresponds to a late peaking CWD signal with high velocity (**B2**, *arrow*). Invasive hemodynamics do not demonstrate a gradient between the LV base and the aorta (AO) **(C1)**. However, upon repositioning the catheter distal to the papillary muscle **(C2)**, the gradient (*red bracket*) is now demonstrated between the apex and base of the LV. The patient underwent septal myectomy via a transapical approach, which allowed better visualization of the midventricular segments and adequate depth of resection. Contact fibrosis was directly visualized (**D**, *arrows*).

reflective of increased velocity and obviates the need to "pulse down" the septum using pulsed-wave Doppler (PWD). Continuous-wave Doppler is crucial for distinguishing fixed obstruction (aortic stenosis/subvalvular membrane) from dynamic LVOT obstruction, as treatment approaches differ. Dynamic obstruction will result in a CWD jet that starts in early systole and with a late peaking concave acceleration curve, often referred to as "dagger shape," although the appearance is closer to that of a nonworking upper edge of a Bowie knife (Figure 1A). In contrast, a fixed obstruction CWD gradient peaks in early-mid systole with a more rounded contour. Gradients >60 mm Hg may result in a "lobster claw" pattern (Figure 3A). This unique Doppler profile reflects a midsystolic drop in apex-to-base blood flow within the LV cavity due to increased downstream impedance at the site of dynamic LV obstruction.[34,35] Pulsed-wave Doppler of the thoracic aorta shows a double-peak contour (Figure 3B), which correlates with the spike-and-dome in the invasive aortic pressure tracing and the bifid peripheral pulse in patients with severe dynamic LVOT obstruction (Figure 3C).

A peak LVOT gradient >30 mm Hg at rest has historically been associated with a 2-fold increase in HCM-related mortality.[36] However, obstruction can be highly dynamic, and relying solely on the presence of LVOT gradients >30 mm Hg at rest can lead to misclassification of patients as being nonobstructive. Provocative maneuvers may be necessary to unmask dynamic LVOT obstruction.[19,37,38]

MIDVENTRICULAR OBSTRUCTION

Hypertrophic cardiomyopathy with MVO is an important subtype of HCM to recognize as it may result in refractory symptoms and be associated with an increased risk of ventricular arrhythmias, mortality,[39] and LV aneurysm with or without thrombus.[39,40] Midventricular obstruction is usually related to hyperkinesia of the mid-LV cavity, resulting in apposition of hypertrophied midseptum and hypertrophied papillary muscles, distinct from SAM of the MV (Figure 4A, Video 2). Color-flow Doppler demonstrates turbulence at the midventricular level, with CWD typically depicting a narrow, late-peaking systolic velocity ("ice pick" appearance; Figure 4B, Video 3). Invasive hemodynamic assessment (Figure 4C) and direct operative visualization (Figure 4D) may provide clinically helpful correlations.

The combination of MVO and apical aneurysm (Figure 5A, Video 4) results in a distinct Doppler profile, often resembling fangs, that is not seen in any other condition (Figure 5B, Video 5). A differential pressure gradient is established across the apical aneurysm, site

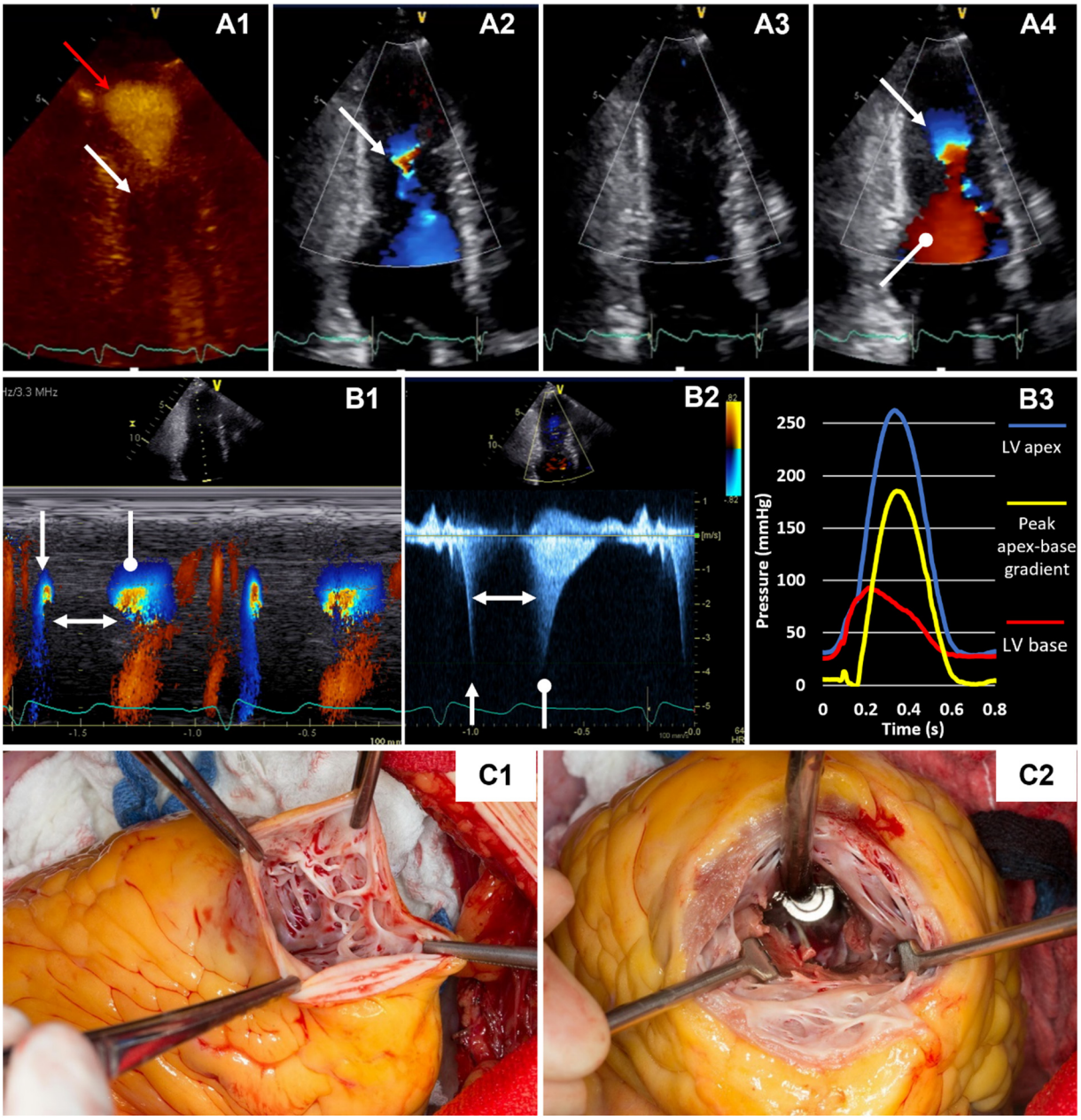

Figure 5 Two-dimensional echocardiography with contrast demonstrates midventricular hypertrophy (**A1**, *white arrow*) and an apical aneurysm without thrombus (**A1**, *red arrow*; Video 4). Color-flow Doppler reveals midventricular flow acceleration in early systole (**A2**, *closed arrow*) followed by complete cessation of flow from the aneurysm in mid-to-late systole **(A3)**. In early diastole **(A4)**, paradoxical forward flow from the apex reemerges (*closed arrow*), colliding with early mitral inflow (*circle head arrow*; Video 5). Color M-mode **(B1)** illustrates the sequence of early systolic apical forward flow (*closed arrow*) and cessation of flow throughout mid-late systole due to midventricular obliteration (*double-headed arrow*), followed by paradoxical diastolic forward flow (*circle head arrow*). In the absence of mid-late systolic flow, Doppler echocardiography shows 2 peaks resembling fangs but does not permit assessment of the peak intracavitary pressure gradient **(B2)**. Invasive hemodynamic measurements reveal very high apical pressures, which may account for the genesis of apical aneurysms **(B3)**. Aneurysmectomy and midventricular myectomy is a potential treatment option for select cases **(C1-2)**.

of MVO, and LV cavity such that CWD interrogation reveals early systolic blood flow acceleration from the apical aneurysm into the midventricle. Early systolic flow acceleration quickly terminates with complete cessation of midventricular blood flow throughout mid to late systole due to severe muscular obstruction and apical akinesia. Blood becomes trapped within the apex at high pressures.[41] With a decline in basal LV cavity pressure, the apex-to-base gradient results in paradoxical flow out of the aneurysmal segment in early diastole.[42] In patients with medically refractory symptoms, myectomy (transaortic, transapical, or combined approach) is effective at relieving MVO (Figure 5C).[43,44]

The vast majority of HCM patients with apical aneurysms have MVO; however, MVO may be present with or without apical aneurysm formation.[45,46] The unique CWD profile described above is a

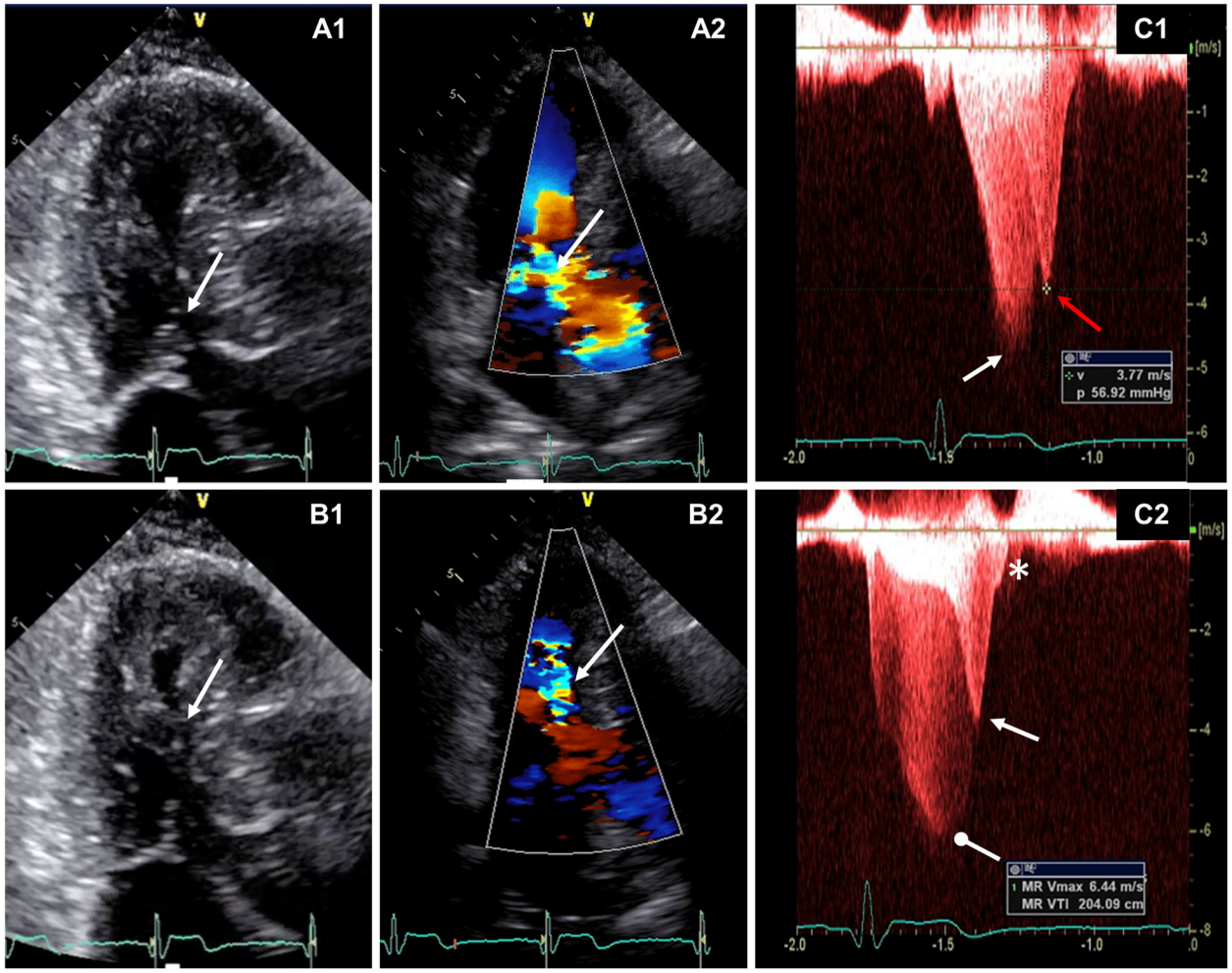

Figure 6 Two-dimensional echocardiography identifies SAM of the mitral leaflets (**A1**, *arrow*) with flow acceleration in the LVOT (**A2**, *arrow*). In late systole, there is MVO due to a prominent papillary muscle abutting the septum (**B1**, *arrow*) with accompanying flow turbulence at midventricular level (**B2**, *arrow*). Continuous-wave Doppler through the LV and LVOT reveals 2 separate late peaking signals **(C1)**. The first peak corresponds to LVOT obstruction (**C1**, *white arrow*), and the second peak corresponds to MVO (**C1**, *red arrow*). Continuous-wave Doppler through the LV and MV shows the MR signal (**C2**, *circle tip arrow*) and the late peaking MVO (**C2**, *arrow*). Differentiation of intracavitary and outflow tract gradients can be challenging; however, the MR peak velocity will always be higher than the LVOT peak velocity and the Doppler envelope characteristic of MVO is very late peaking. The time course of pressure decay also aids interpretation. The LV-left atrial gradient (**C2**, *circle tip arrow*) and the midcavitary gradient (**C2**, *arrow*) both show a stepwise but symmetric decline; the reduction in the midcavitary gradient begins with isovolumic relaxation, and both end with opening of the MV (**C2**, *asterisk*).

sine qua non for the presence of an apical aneurysm and should prompt consideration of echocardiographic image-enhancing agent use and/or CMR.[47] During contrast echocardiography, it is important to obtain views sweeping through the entire apex to avoid missing small and eccentric apical aneurysms.[48] Although classically the diagnostic sensitivity of apical aneurysms in HCM is higher for CMR than for contrast echocardiography, recent data suggest that apical aneurysm detection is equivalent between these 2 modalities in expert centers.[49]

OBSTRUCTION IN SERIES

Color-flow Doppler allows for recognition of tandem stenoses (such as LVOT obstruction in a patient with aortic stenosis or MVO in a patient with LVOT obstruction), and color M-mode is particularly helpful given its superior temporal resolution.[50] However, determining the contribution of each component to the overall gradient may not be possible via echocardiography, prompting invasive hemodynamic assessment.[51] In HCM, the Doppler-obtained peak instantaneous gradient correlates well with the peak instantaneous gradient obtained at cardiac catheterization due to the timing and contour of hemodynamic pressure tracings.[52] The mean gradient should be used to assess severity in fixed obstruction, such as valvular aortic stenosis, since the peak instantaneous gradient usually exceeds the peak-to-peak gradient.[52]

Recognition of multilevel obstruction within the left ventricle (LV), such as MVO coexisting with LVOT obstruction, alters therapeutic decision-making. Thorough assessment of midventricular anatomy and color-flow Doppler should be performed in patients

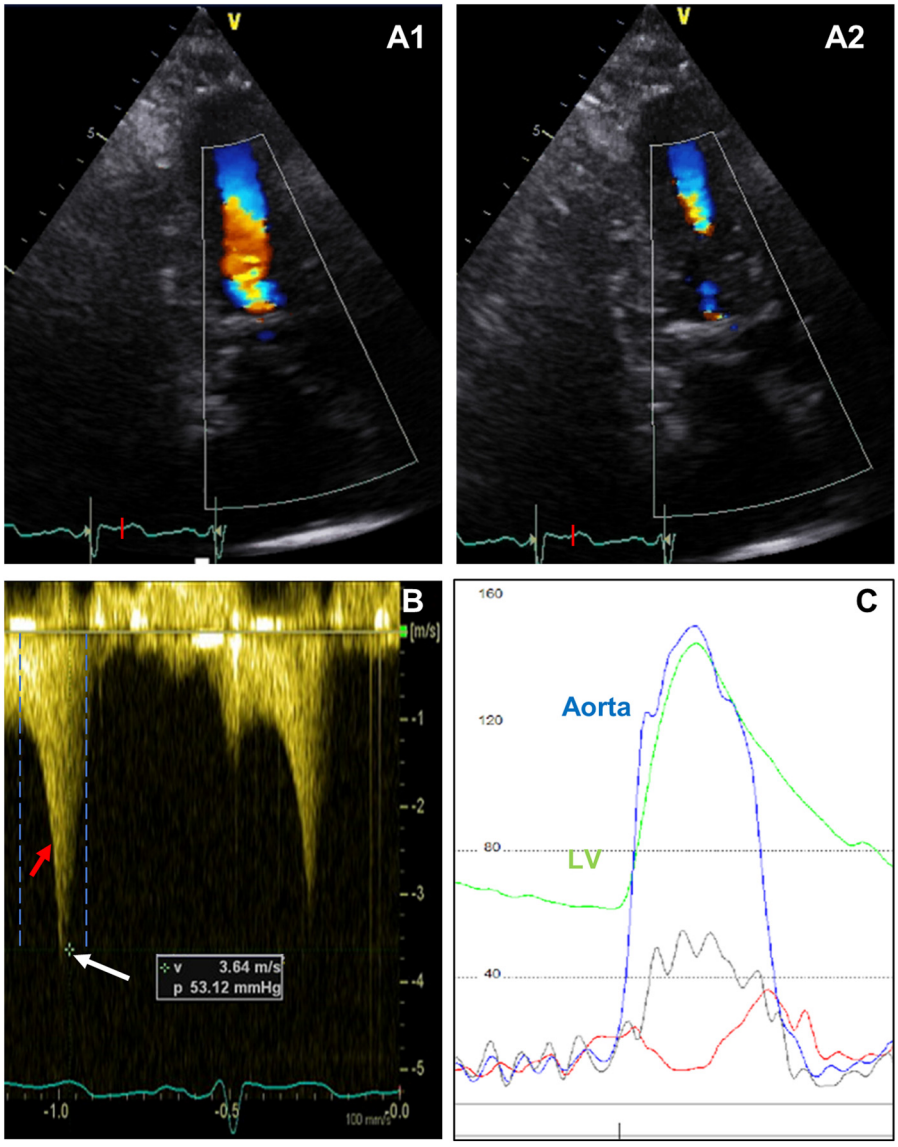

Figure 7 Occasionally, increased intracavitary CWD flow velocities result from hyperdynamic systolic function with cavity obliteration and not true obstruction.[56] This phenomenon is demonstrated with color-flow imaging through the midventricle in the setting of small LV chamber size **(A1-A2)**. Continuous-wave Doppler suggested intracavitary gradients of ~50 mm Hg (**B**, *white arrow*); however, invasive hemodynamic assessment with simultaneous CWD **(C)** confirmed the absence of intraventricular pressure gradients. Another clue to this phenomenon is the rapid downslope of the CWD velocity (**B**, *red arrow*) in midsystole without a late systolic high-velocity "tail" to the CWD contour and the resulting short duration of systole (**B**, *dashed blue lines*).

with LVOT obstruction, both to identify patients with multilevel obstruction (Figure 6) and for recognition of anatomy that may predispose to unmasking MVO after LVOT gradient reduction. Alcohol septal ablation is a treatment option for isolated LVOT obstruction but should not be utilized when there is multilevel obstruction. Currently, mavacamten, an oral cardiac-specific myosin inhibitor, has been approved by the Food and Drug Administration only for treatment of patients with LVOT obstruction.[53] However, a study of patients without LVOT obstruction (but including isolated MVO) is in progress.[54] In patients with multilevel obstruction and medically refractory symptoms, septal myectomy (transaortic, transapical, or combined approach) remains the treatment of choice.[39,41]

NONOBSTRUCTIVE HCM AND PROVOCATION OF OBSTRUCTION

Approximately one-third of patients with HCM are nonobstructive.[1,20] Differences in structure and intrinsic geometry of the LVOT, the intraventricular septum, and the MV apparatus may cause the absence of obstruction.[7,21,55] Patients who are initially nonobstructive may develop dynamic obstruction at future assessment. True obstruction must be distinguished from hyperdynamic LV systolic function resulting in increased intracavitary velocities and/or cavitary obliteration via utilization of both color Doppler and CWD (Figure 7A and B).[56] When hemodynamics are unclear, invasive assessment with concurrent TTE should be utilized to confirm the diagnosis (Figure 7C). Despite

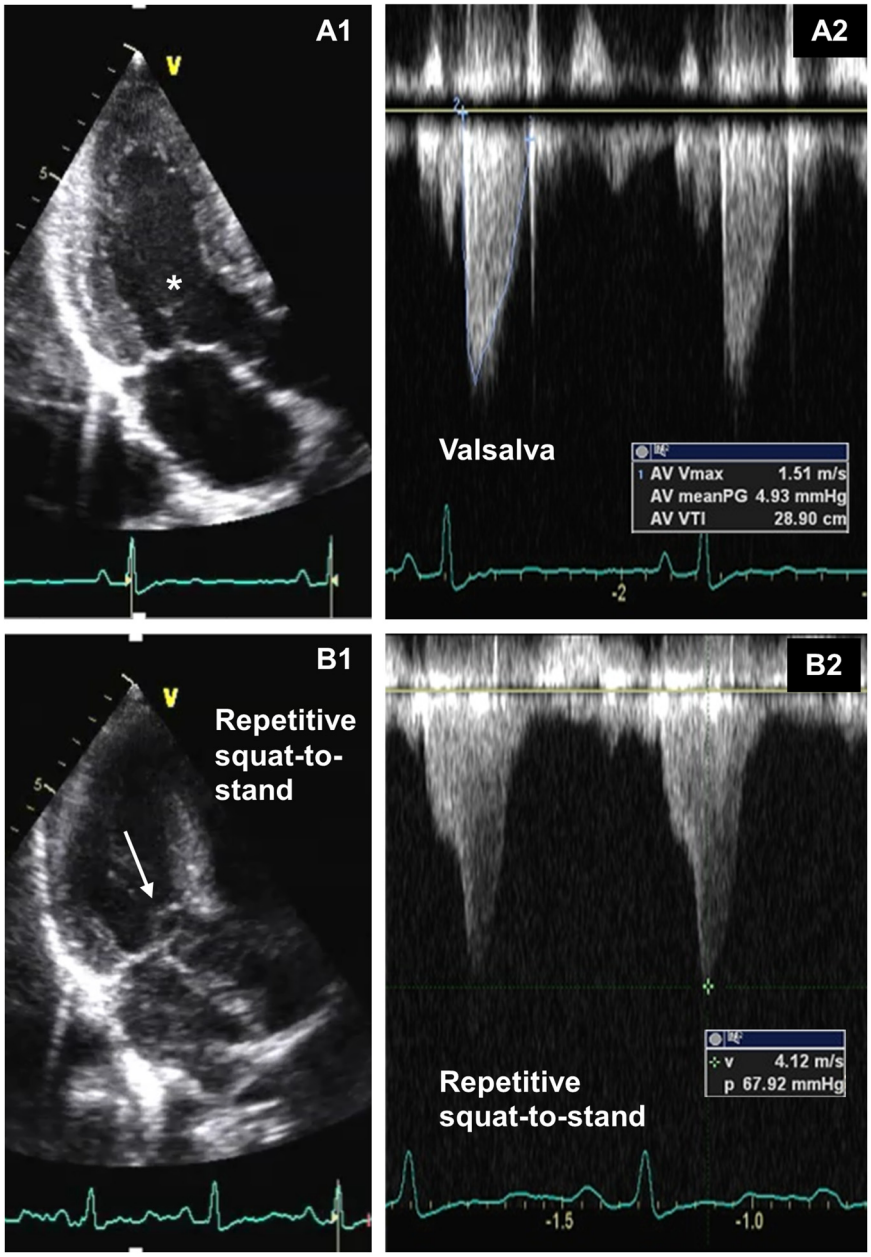

Figure 8 Asymmetric septal hypertrophy and elongated mitral leaflets (*asterisk*) are present **(A1)** without SAM of the MV at rest or with Valsalva maneuver (**A2**, Video 6). Valsalva maneuver has excellent specificity but limited sensitivity for detecting LVOT obstruction. After repetitive squat-to-stand, SAM (**B1**, *arrow*, Video 7) and dynamic LVOT obstruction on CWD Doppler (**B2**, Video 8) were easily induced (peak gradient, 68 mm Hg). Other clinically useful methods for assessing latent LVOT obstruction in our clinical practice include inhaled amyl nitrite during echocardiography, treadmill stress echocardiography, and post-premature ventricular contraction or isoproterenol during invasive hemodynamic assessment.

the lack of obstruction, nonobstructive HCM is not a benign entity and has been associated with adverse outcomes, including a low output state with progressive diastolic dysfunction, heart failure with preserved ejection fraction,[57] and sudden cardiac death.[58,59]

Decreases in preload, decreases in afterload, and increases in contractility promote obstruction. The postprandial state is known to provoke dynamic obstruction and may be employed clinically to unmask latent obstruction.[60-62] Mesenteric vasodilation postprandially results in decreased peripheral vascular resistance, augmenting stroke volume akin to use of an arterial vasodilator.[63] Compensatory increases in heart rate and mesenteric pooling of blood may also reduce preload, resulting in reduced stroke volume, further worsening dynamic LVOT obstruction.[60-62]

If a significant resting gradient within the LV is not present in a patient with HCM, a systematic approach is needed to rule out provocable obstruction. Valsalva maneuver, which decreases preload, is the first step in attempts to provoke obstruction and should be routinely performed in all patients with HCM. When significant obstruction has not been revealed with Valsalva maneuver, we routinely include repetitive squat-to-stand into our standard resting TTE assessment of HCM. We have found a repetitive squat-to-stand maneuver to be more sensitive than Valsalva maneuver for the frequency and severity

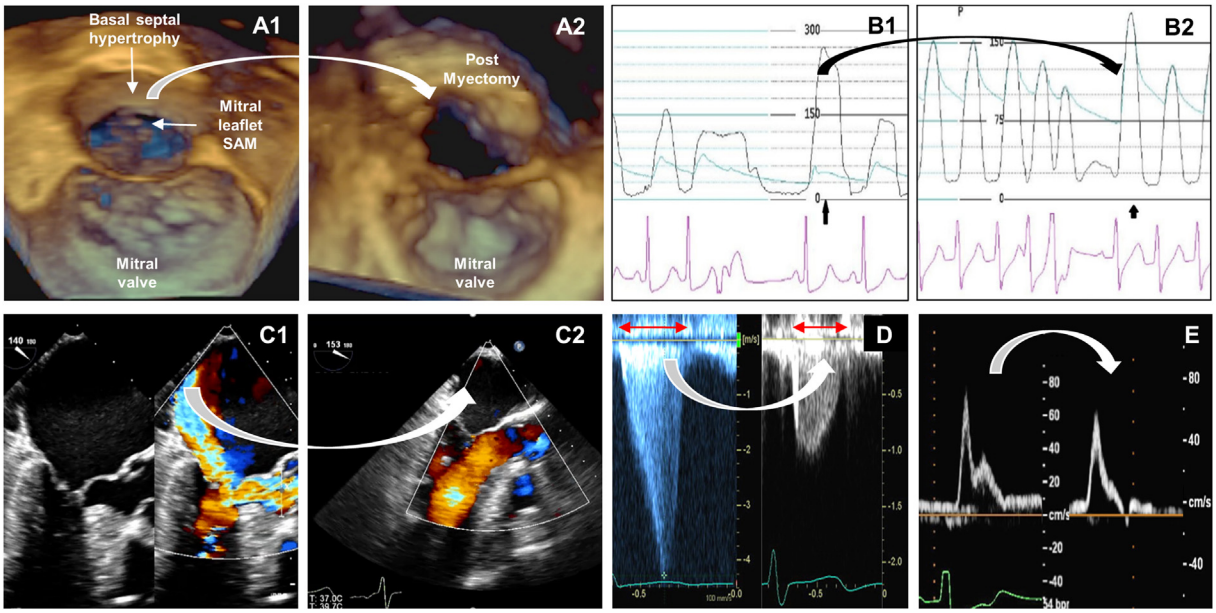

Figure 9 Three-dimensional echocardiography from the perspective of looking through the aortic valve into the LVOT shows septal hypertrophy and SAM of the MV leaflets with severe LVOT obstruction **(A1)**. Post–septal myectomy, the LVOT is enlarged without SAM or LVOT obstruction at rest or post-premature ventricular contraction **(A2)**. Intraoperative measurement of LVOT gradient via needles in the aorta and LV both preoperatively **(B1)** and postoperatively **(B2)** complements TEE findings and is helpful when Doppler gradients are difficult to obtain.[53] Following successful myectomy, there is resolution of SAM-mediated MR (**C1-2**, Videos 9-11). The improvement in LVOT gradients also corresponds with shortening of the systolic ejection period (**D**, *red arrows*). Pulsed-wave Doppler of abdominal aortic flow velocity shows conversion from the bifid contour pulse to normal aortic flow **(E)**.

of provocable obstruction (Figure 8, Videos 7-8).[64] Repetitive squat-to-stand effectively lowers preload and afterload without requiring any special equipment or medication use. Inhalation of amyl nitrite, which decreases preload and afterload through venodilation and arterial dilation, is also utilized for provocation of obstruction at resting TTE. Our utilization of amyl nitrite has substantially declined given the effectiveness of the repetitive squat-to-stand maneuver and intermittent national shortages of amyl nitrite. If the aforementioned approaches fail to elicit a gradient and suspicion remains high for the presence of dynamic obstruction contributing to symptoms, then exercise echocardiography should be considered to assess for the presence of dynamic LVOT obstruction.[65,66] Postprandial exercise testing has been shown to have benefit over fasting exercise in some patients.[61] If noninvasive approaches fail to reveal clinically suspected obstruction, hemodynamic cardiac catheterization with isoproterenol and/or exercise may be required to elicit a gradient.[67] Finally, it is critical to remember that obstruction with HCM is not only dynamic but extremely variable and may fluctuate on a day-to-day basis[37] between Doppler echocardiography and invasive hemodynamic assessment[38] and even during a single invasive hemodynamic assessment.[19]

ECHOCARDIOGRAPHIC ASSESSMENT OF TREATMENT RESPONSE

Mavacamten

Mavacamten is a potent negative inotrope proven to reduce LVOT gradients in HCM with LVOT obstruction.[68] Serial echocardiographic assessment of LVOT gradient, both at rest and with the Valsalva maneuver, is needed to guide dose titration in patients utilizing mavacamten. Transthoracic echocardiography must be conducted at weeks 4, 8, and 12 after initiation of treatment and every 12 weeks thereafter both for gradient monitoring and to assess for LV systolic dysfunction, as part of the Risk Evaluation and Mitigation Strategy program for mavacamten. Should a dose titration occur, echocardiography must also be repeated 4 weeks thereafter. How to incorporate provocative maneuvers beyond Valsalva into the chronic management of mavacamten remains unclear.

Myectomy

In HCM patients with medically refractory symptoms driven by severe LVOT obstruction, septal reduction therapy should be considered, via either septal myectomy or septal alcohol ablation. Echocardiography is central to evaluation of procedural candidacy, intraprocedural anatomy and hemodynamics, and postprocedure follow-up. Preoperative TTE allows for anatomical definition obstruction, including the interventricular septum, anterior MV leaflet, chordae tendineae, and papillary muscles. Understanding the extent and morphology of LVH is important for surgical planning. Prebypass TEE allows anatomic definition of the LVOT (Figure 9A) as well as exclusion of primary MV abnormalities that may coexist with SAM in up to 20% of patients, given the potential to alter the surgical approach.[28,30-32,69] Presence and degree of aortic regurgitation should be assessed due to the potential risk of aortic valve during myectomy.[70] Transesophageal echocardiography may be utilized in combination with direct needle measurement of pressures following sternotomy (Figure 9B), with utilization of isoproterenol or mechanical cardiac stimulation for premature ventricular complexes, to confirm the presence and location of dynamic obstruction.[69] Postbypass TEE should be routinely performed to assess for residual LVOT gradient, residual or unmasked MVO, iatrogenic ventricular

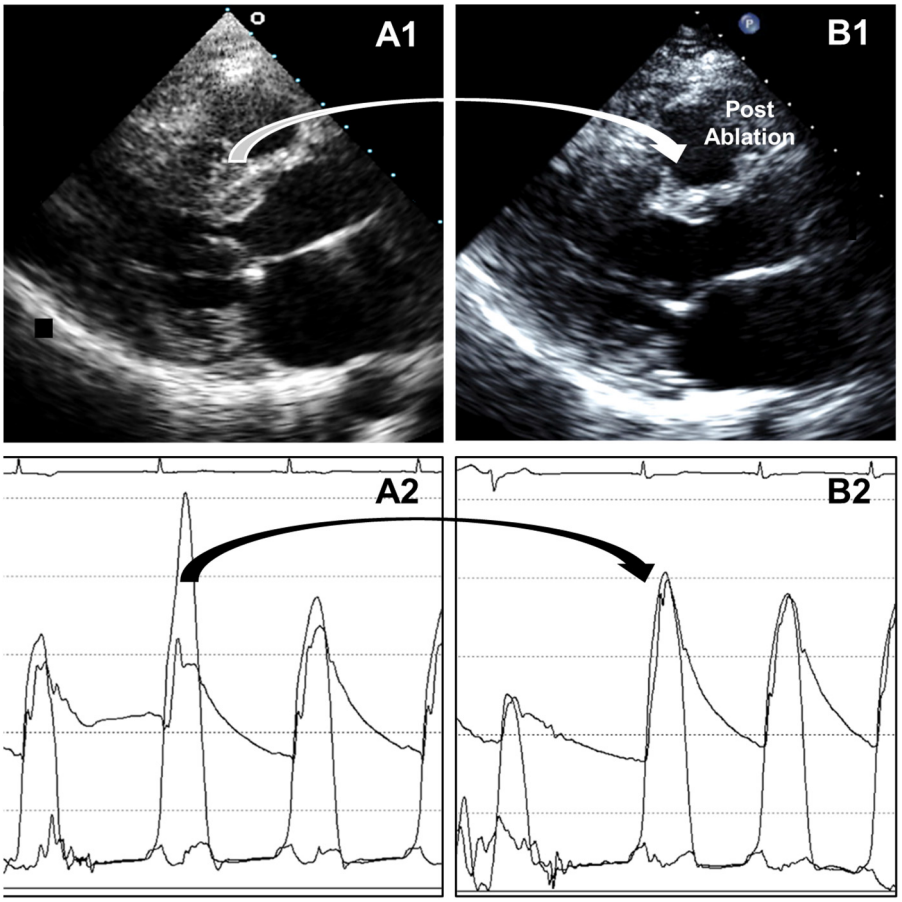

Figure 10 Parasternal long-axis view echocardiographic image shows asymmetric septal hypertrophy with dynamic LVOT obstruction (**A1-2**, Video 12). Immediately after alcohol septal ablation there is myocardial stunning of the basal septum followed by localized remodeling in the ensuing weeks to months (**B1**, Video 13). Invasive pressure measurements demonstrate absence of LVOT gradients **(B2)**.

septal defect (which must be distinguished from unroofed septal perforators, which will only have diastolic flow), new-onset or worsening aortic regurgitation, MV SAM, degree of MR (Figure 9C, Videos 9-11), and biventricular systolic function.[69] Following septal myectomy, continued assessment of Doppler hemodynamics is utilized to guide clinical management (Figure 9D and E).

Alcohol Septal Ablation

Intraprocedural TTE is utilized during alcohol septal ablation (Figure 10A, Video 12) to assess for distribution of echocardiographic imaging enhancement agent given via intracoronary injection, with careful inspection of the papillary muscles, right ventricle, nontargeted septum, and lateral wall as structures to be avoided.[71] Postprocedure (Figure 10B, Video 13), two-dimensional (2D) appearance of the septum, the degree of LVOT obstruction, SAM, and MR must also be assessed utilizing color-flow Doppler and CWD. Care should be taken to assess the midventricle for unmasked MVO, with consideration of color M-mode utilization.

FUTURE DIRECTIONS

Doppler echocardiography continues to evolve. Technical improvements in probes and echocardiographic systems may yield further increases in temporal resolution of 2D color Doppler, allowing for better characterization of complex obstruction currently requiring color M-mode. Beyond 2D advancements, evolution of three-dimensional (3D) color Doppler is certain to continue to shift the landscape of echocardiographic imaging. Having the ability to obtain a high temporal resolution color 3D volume of the entire LV would eliminate the possibility of sampling error and further elucidate the complex interplay of ventricular flow in patients with HCM. Alongside these technical advancements, we foresee continuous growth in the role of machine learning and artificial intelligence for interpretation of Doppler data, whether it be continuous-wave sampling of gradients, 2D characterization of Doppler flow, or 3D color volume mapping. Among other advances, this may clarify quantitation of obstruction in series, a problem that continues to rely upon invasive hemodynamic assessment in some cases.[72]

CONCLUSION

Echocardiography is essential in the diagnosis, follow-up, and procedural planning in patients with HCM. An organized assessment is essential, as obstruction has many faces. Anatomic evaluation must include quantitation and characterization of LVH as well as comprehensive evaluation of the MV and subvalvular apparatus abnormalities. Although dynamic obstruction classically occurs at the level of the LVOT, care must be taken to evaluate for MVO or other intracavitary

instruction, either in isolation or in series. Provocation requires a sequential approach to ensure that occult LVOT or midventricular obstruction is not missed. Doppler imaging techniques provide invaluable diagnostic and prognostic information that dictates management, prognostication, procedural guidance, and follow-up in HCM.

REVIEW STATEMENT

Given her role as JASE Editor-in-Chief, Patricia A. Pellikka, MD, had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Allan L. Klein, MD.

CONFLICTS OF INTEREST

None.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2024.02.010.

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